

# Exhibit G

**SUPPLEMENTAL REPORT OF PEGGY PENCE, PhD, RAC, FRAPS  
GYNECARE PROLIFT TOTAL, ANTERIOR, AND POSTERIOR PELVIC FLOOR  
REPAIR SYSTEMS AND GYNECARE PROSIMA PELVIC FLOOR REPAIR SYSTEMS  
RE: ETHICON, INC., ETHICON WOMEN'S HEALTH AND UROLOGY, a Division of  
Ethicon, Inc., GYNECARE, AND JOHNSON & JOHNSON  
(Collectively referred to in this Report as Ethicon)**

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## **I. REPORT OBJECTIVES**

Since the preparation of my prior Reports regarding GYNECARE PROLIFT Total, Anterior, and Posterior Pelvic Floor Repair Systems (referred to herein as PROLIFT) (Report dates: June 15, 2012; November 9, 2012 [Supplemental]; November 12, 2012 [Second Supplemental]; July 17, 2014) and GYNECARE PROSIMA Pelvic Floor Repair Systems (referred to herein as PROSIMA) (Report date: February 1, 2016), I have had an opportunity to review the November 12-13, 2015, deposition of Martin Weisberg, M.D., and associated exhibits. Dr. Weisberg testified as the Ethicon Corporate Designee regarding Revised TVT Instructions for Use (IFUs) and Revised Gynemesh PS IFUs. The purpose of this Supplemental Report is to present information from the stated Ethicon deposition and other pertinent information that provide further support for my previously expressed opinions. I have not changed any of my opinions as a result of my review of these additional materials, nor do I offer any new opinions in this Supplemental Report. Importantly, my prior Reports, specified above, are incorporated herein by reference in their entirety, including all opinions expressed therein.

The method and level of scrutiny that I used in preparing this Supplemental Report are the same that I have used in my practice for my entire career as an expert in medical product development, regulatory affairs, and as a scientist, and the same that I used in the preparation of my prior Reports referenced above. To facilitate review and cross-reference to my prior June 15, 2012, July 17, 2014, and February 1, 2016, Reports, the supplemental information provided herein is presented in the same order as presented in those Reports.

## **II. APPLICABLE INDUSTRY STANDARDS**

**(Attached as Exhibit 1 and incorporated as if set forth fully herein)**

Globally recognized industry standards for the development of medical devices and, in particular, those relevant to the subject matter of both this Supplemental Report and my prior Reports (PROLIFT: June 15, 2012; November 9, 2012 [Supplemental]; November 12, 2012 [Second Supplemental]; and July 17, 2014; PROSIMA: February 1, 2016) are described and establish additional foundation for my opinions, notably, other than FDA regulations and guidance.

## **III. CLINICAL BACKGROUND UNDERLYING OPINIONS: MULTIPLE AUTHORITATIVE BODIES SUPPORT NEED FOR CLINICAL DATA FOR MESH USE IN TRANSVAGINAL PELVIC ORGAN PROLAPSE (POP) REPAIR**

The purpose of clinical evaluation of a medical device is to demonstrate that the device complies with the essential principles of safety and performance, including that any adverse events are acceptable when weighed against the benefits of the device's intended performance.<sup>1</sup> This is especially important for a device that is intended to treat quality of life symptoms and for which there are alternative treatments. While clinical evaluation (Reference Exhibit 1, Section II.F.) should be performed premarketing, clinical evaluation also should be conducted periodically throughout the life cycle of the device to (i) analyze the product's risk-benefit ratio in consideration of available clinical safety and performance information and (ii) take actions as appropriate. Among such actions are generation of clinical data to address outstanding issues

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<sup>1</sup> Final Document: Global Harmonization Task Force. Clinical Evaluation, May 2007, Section 1.

and the need to include risk information identified in the risk analysis in the Instructions for Use.<sup>2</sup>

Multiple authoritative sources have emphasized the importance of clinical studies to establish the safety and effectiveness of vaginal mesh implants and, accordingly, have expressed concern about the lack of clinical data to support permanent implantation of vaginal mesh for POP repair and establish whether the benefit-risk ratio is favorable. Among such authoritative sources are those discussed below.

**A. Haute Autorité de Santé (HAS) French National Authority for Health. Evaluation of Mesh Implants Installed Through the Vaginal Approach in the Treatment of Genital Prolapse. Department of the Evaluation of Medical and Surgical Procedures.**

Please reference my February 1, 2016, PROSIMA Report (Section III.A.2.) for a discussion of this Evaluation. As noted in my PROSIMA Report, the overall conclusion of the HAS Evaluation was that the available data in the literature at the time the HAS report was written did not allow an effective evaluation of the anatomical and functional viability of transvaginally placed implants for the treatment of genital prolapse. Serious complications were identified but their frequency was not able to be determined. **Therefore, the French National Authority for Health concluded that the use of mesh implants for transvaginal correction of genital prolapse remained a matter of clinical research.** It is important to note that the date of this conclusion was November 2006, approximately 20 months after the PROLIFT became available for sale and the same month in which Ethicon sought to market the PROSIMA. (Emphasis added.)

**B. United States Food and Drug Administration (FDA) Literature Review and MAUDE Database Review**

Please reference my February 1, 2016, PROSIMA Report (Section III.A.3.) for a discussion of the results of the U.S. FDA's systematic review of the scientific and medical literature for repair of POP with surgical mesh from 1996-2011 and MAUDE (Manufacturer and User Facility Device Experience) Database reviews from 2005-2007 and 2008-2010. Please also reference my February 1, 2016, PROSIMA Report (Section VI.E.) for a discussion of FDA's reclassification of vaginal mesh for POP repair to Class III with requirement for PMA application. Thus, if Ethicon were to seek to market the PROLIFT or PROSIMA today, the company would be required to conduct the appropriate clinical study(ies) and demonstrate safety and effectiveness and a favorable benefit-risk ratio or the product would not be allowed to reach the market.

**C. National Institute for Health and Clinical Excellence: Interventional Procedure Guidance RE: Surgical Repair of Vaginal Wall Prolapse Using Mesh**

It is noteworthy that in June 2008, after conducting a systematic review of published evidence, the National Institute for Health and Care Excellence (NICE) in the United Kingdom issued a Guidance on the use of mesh for treating vaginal wall prolapse.<sup>3</sup> Included in the systematic review were 30 studies on the use of mesh for anterior repair, involving 2,472 women; nine

<sup>2</sup> Final Document: Global Harmonization Task Force. Clinical Evaluation, May 2007, Section 1.

<sup>3</sup> National Institute of Health and Clinical Excellence. Surgical repair of vaginal wall prolapse using mesh. June 2008. Interventional Procedure Guidance (IPG) 267.

studies, involving 417 women, on the use of mesh for posterior repair; and 14 studies, involving 1,680 women, on the use of mesh in anterior and/or posterior repair. These included a total of 18 randomized controlled trials (seven of which were available as conference abstracts only), seven non-randomized comparative trials, three registry studies, and 25 case series. Meshes studied included absorbable synthetic mesh (seven studies), absorbable biological mesh (17 studies), combined synthetic and biological mesh (three studies), non-absorbable synthetic mesh (26 studies), and more than one of the noted types of mesh (three studies). Median follow-up was 12 months (range: one to 17 months), 13 months (range: one to 51 months), and 14 months (range: one to 38 months) for the studies of mesh for posterior repair, anterior and/or posterior repair, and anterior repair, respectively.

Interpretation of the data was difficult because of the different meshes used and variations in surgical approach. NICE reported that the evidence suggested that surgical repair of vaginal wall prolapse using mesh may be more efficacious than traditional surgical repair without mesh, but both efficacy and safety vary with different types of mesh, and data on long-term efficacy are limited. Importantly, due to the risks of complications that can cause significant morbidity, NICE advised that **“this procedure only should be used with special arrangements for clinical governance, consent and audit or research.”**<sup>4</sup> (Emphasis added.) They further stressed that patients should be provided with clear written information that ensures they understand that there is uncertainty about long-term results and that there is a risk of complications, including sexual dysfunction and erosion into the vagina, that may require additional procedures.<sup>5</sup>

**D. 2nd International Urogynecological Association Grafts Roundtable Publishes Consensus on Need for Research and Minimum Standards for Mesh Use in Transvaginal Procedures**

In 2012, the consensus of the 2<sup>nd</sup> International Urogynecological Association Grafts Roundtable conference (2010) was published on the subject of “[o]ptimizing safety and appropriateness of graft use in transvaginal pelvic reconstructive surgery,”<sup>6</sup> which noted that numerous new implants and ancillary devices had been introduced to the market in the prior 10 years “with **little or no clinical data or research.**”<sup>7</sup> The authors proposed that **minimum standards should be demanded for new products prior to marketing**, including accurate data on the physical properties of the product, data on biological properties obtained following implantation in high-quality animal studies, anatomical studies on cadavers, and **“upfront clinical studies followed by a compulsory registry on the first 1,000 patients implanted. Ideally, manufacturers should support well-designed prospective (randomized) clinical trials that can support the claimed benefits of the new product.”**<sup>8</sup> (Emphasis added.)

<sup>4</sup> National Institute of Health and Clinical Excellence. Surgical repair of vaginal wall prolapse using mesh. June 2008. Interventional Procedure Guidance (IPG) 267.

<sup>5</sup> *Id.*

<sup>6</sup> Slack M et al. A standardized description of graft-containing meshes and recommended steps before the introduction of medical devices for prolapse surgery (data presented at 2<sup>nd</sup> IUGA Grafts Roundtable June 2010). *Int Urogynecol J* 2012;DOI 10.1007: s00192-012-1678-2.

<sup>7</sup> *Id.*

<sup>8</sup> *Id.*

**E. Committee Opinion of ACOG and AUGS Regarding Vaginal Placement of Synthetic Mesh for Pelvic Organ Prolapse**

Please reference my February 1, 2016, PROSIMA Report (Section III.A.6.) for a discussion of the joint opinion of the American College of Obstetricians and Gynecologists (ACOG) and the American Urogynecologic Society (AUGS) as regards vaginal placement of synthetic mesh for pelvic organ prolapse repair, issued in December 2011 and reaffirmed in 2015.

**IV. CHANGES TO GYNEMESH PS INSTRUCTIONS FOR USE (IFU), 2014-2015, RELEVANT TO PROLIFT AND PROSIMA OPINIONS**

In a letter dated March 24, 2014, the Therapeutics Products Directorate, Medical Devices Bureau, Health Canada, requested Johnson & Johnson Medical Products to provide Additional Information under Section 39 of its *Medical Devices Regulations* in regards to the company's "*Surgical Meshes for Pelvic Organ Prolapse (POP)*," remarking that information recently brought to the Bureau's attention indicated that these devices "may not meet the safety and effectiveness requirements of the *Medical Devices Regulations* (the Regulations)."<sup>9</sup> Specifically, as it pertains to the subject matter of this Supplemental Report, Health Canada requested up-to-date labeling to include, but not limited to, the following potential complications/adverse events, advising that "[c]linical evidence has demonstrated that the use of surgical mesh for the treatment of pelvic organ prolapse (POP) has the potential to lead to [these] adverse events":

"mesh extrusion, exposure, or erosion; acute or chronic pain; dyspareunia; mesh contracture and its sequelae (including vaginal tightening and/or shortening); vaginal scarring; infection; organ perforation; neuromuscular damage; bleeding or hemorrhage; recurrence of prolapse; defecatory dysfunction; voiding dysfunction; and other urinary problems. In addition, one or more revision surgeries may be necessary to treat these complications, while some complications may not always be completely corrected."<sup>10</sup>

Health Canada instructed that if any of the above potential complications/adverse events had been omitted previously, the labeling should be revised to include them.<sup>11</sup>

Subsequent to this request, over the next approximately 14-15 months, Ethicon undertook to revise its Instructions for Use (IFU) globally for Gynemesh PS, notably, in response not only to Health Canada but also to the Australian TGA's (Therapeutic Goods Administration) "URGENT" request for changes to labeling on October 17, 2014.<sup>12</sup> Specifically, TGA notified Ethicon that the Gynemesh PS IFU needed to appropriately identify risks and detailed items that were either not already included and/or were not sufficiently prominent in the IFU. The matters to be addressed in the IFU included a clear discussion of risk of erosion in a prominent section, with comment regarding patient selection and factors that may increase the likelihood of complications such as erosion. Additionally, TGA requested that the IFU include a **complete**

<sup>9</sup> ETH.MESH.16357665-666: March 24, 2014, Letter to Jerry Gee, Regulatory Affairs Specialist, Johnson & Johnson Medical Products, Markham, ON, from Medical Devices Bureau, Health Canada, Re: Request for Additional Information under Section 39 of the *Medical Devices Regulations*.

<sup>10</sup> ETH.MESH.16357665 at 666-667: *Id.*

<sup>11</sup> ETH.MESH.16357665 at 667: *Id.*

<sup>12</sup> Dr. Martin Weisberg November 12-13, 2015, deposition: Exhibit D-9: 6-page document labeled "Chronology."

**description of all known complications**, including ongoing pain that may not be resolved on explant and other complications identified in the clinical literature, risk assessment documentation, and post-market data submitted to TGA in relation to the device. TGA further noted that these deficiencies “are considered to be breaches of compliance with one or more of the Essential Principles.”<sup>13</sup> TGA’s immediate concern was to ensure risk reduction activities related to device safety were put in place.<sup>14</sup> (Emphasis added.) Of note, the revised IFU became available on Ethicon’s physician website on May 1, 2015.<sup>15</sup>

These requests for changes to the Gynemesh PS labeling are relevant to my opinions as discussed in my prior PROLIFT and PROSIMA Reports, specified above, for the following reasons. Safety information that Health Canada and TGA requested Ethicon to add to the Gynemesh PS IFU is consistent with safety information that my prior PROLIFT and PROSIMA Reports discussed as missing from the product IFUs. Of further note, TGA requested inclusion of all known complications identified in the clinical literature, risk assessment documentation, and post-market data, which were sources that I also evaluated to assess safety information missing from the product IFUs. Thus, both Health Canada’s request and TGA’s request for labeling changes provide corroboration from authoritative bodies of my prior opinions as regards missing safety information and efforts that should have been implemented to manage risk. Dr. Weisberg testified that the adverse reactions that are listed in the 2015 revised IFU for Gynemesh PS would be applicable and accurate for the PROLIFT.<sup>16</sup>

Additionally, Ethicon added other adverse reactions that I had enumerated or discussed as missing safety information in my prior PROLIFT and PROSIMA Reports to the revised Gynemesh PS IFU implemented in 2015. Of note, although safety information specified as missing from IFUs in my prior Reports was included in the revised 2015 Gynemesh IFU, my opinions remain the same as regards other labeling deficiencies or safety information which was previously discussed in my prior Reports as missing from PROLIFT and PROSIMA IFUs but which was not included in the 2015 revised Gynemesh IFU.

## **V. ADVERSE MEDICAL DEVICE EVENT REPORTING: MAUDE DATABASE**

Adverse event databases, such as the MAUDE Database, provide real world clinical experience that contributes useful information about device safety and performance. This information should be considered as part of the ongoing clinical evaluation and risk analysis process for the life cycle of the device, and actions should be taken as appropriate to manage risk, e.g., updating safety information in the Instructions for Use. (Reference Exhibit 1, Section II.G.) Accordingly, Exhibit 2 provides a current overview of the results of MAUDE Database searches for total number of medical device reports from 1999 through 2015 for Ethicon and a number of competitor surgical mesh devices marketed for the repair of SUI and POP. The significance of the large number of adverse event reports is highlighted by the industry-accepted recognition that there is vast underreporting of device-related problems, with estimates that as few as 1 in 100 medical device reportable events is actually reported. (Reference Exhibit 1, Section III.)

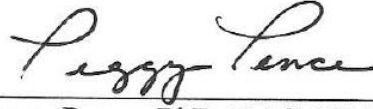
<sup>13</sup> ETH.MESH.24257904 at 911-914: Email October 17, 2014, from Patrick O’Meley, TGA, Subject: for your URGENT attention – Urogynaecological Surgical Mesh Review – Outcomes and actions.

<sup>14</sup> ETH.MESH.24257904 at 912: *Id.*

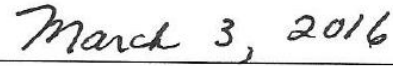
<sup>15</sup> Dr. Martin Weisberg November 12-13, 2015, deposition: Exhibit D-9: 6-page document labeled “Chronology.”

<sup>16</sup> Dr. Martin Weisberg November 12, 2015, deposition, 95:13-16, 19.

I reserve the right to amend or supplement this Report in the event that additional pertinent information becomes available or additional issues are raised in reports of other experts.

A handwritten signature in cursive script that reads "Peggy Pence".

Peggy Pence, PhD, RAC, FRAPS

A handwritten date in cursive script that reads "March 3, 2016".

Date